

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C08G 63/00, 63/02, 67/00, 69/00		A1	(11) International Publication Number: WO 99/12990
			(43) International Publication Date: 18 March 1999 (18.03.99)
(21) International Application Number: PCT/US98/18816		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 10 September 1998 (10.09.98)			
(30) Priority Data: 60/058,328 10 September 1997 (10.09.97) US			
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/058,328 (CON) Filed on 10 September 1997 (10.09.97)			
(71) Applicant (for all designated States except US): RUTGERS, THE STATE UNIVERSITY [US/US]; Old Queens, Somerset Street, New Brunswick, NJ 08903 (US).		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(72) Inventor; and			
(75) Inventor/Applicant (for US only): UHRICH, Kathryn [US/US]; 920 Bloomfield Street, Hoboken, NJ 07030 (US).			
(74) Agent: BUTCH, Peter, J., III; Synnestvedt & Lechner LLP, 2600 Aramark Tower, 1101 Market Street, Philadelphia, PA 19107-2950 (US).			

(54) Title: POLYANHYDRIDES WITH THERAPEUTICALLY USEFUL DEGRADATION PRODUCTS



(57) Abstract

An aromatic polyanhydride having a repeating unit with structure (I) wherein Ar is a substituted or unsubstituted aromatic ring and R is a difunctional organic moiety substituted on each Ar ortho to the anhydride group. Ortho-substituted bis-aromatic dicarboxylic acid anhydride monomers and ortho-substituted bis-aromatic dicarboxylic acid intermediates thereof are also disclosed, as well as implantable medical devices, such as scaffolding implants for tissue reconstruction, drug delivery systems prepared from the aromatic polyanhydrides, as well as therapeutic oral dosage forms and treatment methods.

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

- 1 -

**POLYANHYDRIDES WITH THERAPEUTICALLY
USEFUL DEGRADATION PRODUCTS**

TECHNICAL FIELD

The present invention relates to biocompatible aromatic polyanhydrides having improved degradation properties and processability and unique therapeutic properties. In particular, the present invention relates to aromatic polyanhydrides produced from ortho-substituted bis-aromatic carboxylic acid anhydrides. The present invention also relates to ortho-substituted bis-aromatic dicarboxylic acids useful in the preparation of the aromatic polyanhydrides of the present invention.

BACKGROUND ART

Biocompatible and biodegradable aromatic polyanhydrides are disclosed by U.S. Patent Nos. 4,757,128 and 4,997,904. However, unless incorporated into a copolymer containing a more hydrophilic monomer, such as sebacic acid, the aromatic polyanhydrides of the prior art have slow degradation times as

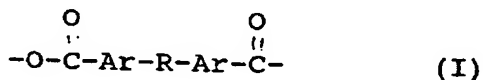
well as relatively insoluble degradation products. A major drawback to the prior art aromatic polyanhydrides is their insolubility in most organic solvents.

Biocompatible and biodegradable aromatic polyanhydrides prepared from para-substituted bis-aromatic dicarboxylic acids are disclosed by U.S. Patent No. 5,264,540. The para-substitution pattern results in higher melt and glass transition temperatures and decreased solubility, thus ultimately making these para-substituted polymers difficult to process.

A need exists for biocompatible and biodegradable aromatic polyanhydrides having improved degradation and processing properties, as well as therapeutic utilities.

SUMMARY OF THE INVENTION

This need is met by the present invention. It has now been discovered that the preparation of aromatic polyanhydrides from ortho-substituted bis-aromatic carboxylic acid anhydrides disrupts the crystallinity of the resulting polymer, enhancing solubility and processability, as well as degradation properties. Therefore, according to one aspect of the present invention, an aromatic polyanhydride is provided having a repeated unit within the structure of Formula I:



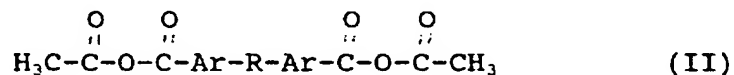
wherein Ar is a substituted or unsubstituted aromatic ring and R is a difunctional organic moiety substituted on each Ar ortho to the anhydride group. Ar and R are preferably selected so that the hydrolysis products of the polyanhydrides have a chemical structure resembling pharmaceutically-active materials, particularly salicyclates such as aspirin, non-steroidal anti-inflammatory naphthyl or phenyl propionates such as ibuprofen, ketoprofen, naproxen, and the like, or

other aromatic anti-inflammatory compounds such as indomethacin, indoprofen, and the like. In particular, Ar is preferably a phenyl group and R is preferably $-Z_1-R_1-Z_1-$ in which R_1 is a difunctional moiety and both Z_1 's are

5 independently either an ether, ester, amide, anhydride, carbonate, urethane or sulfide groups. R_1 is preferably an alkylene group containing from 1 to 20 carbon atoms, or a group with 2-20 carbon atoms having a structure selected from $(-CH_2-CH_2-O-)_m$, $(-CH_2-CH_2-CH_2-O-)_m$, and $(-CH_2-CH(CH_3)-O-)_m$.

10 Ortho-substituted bis-aromatic carboxylic acid anhydrides of the present invention are novel and non-obvious intermediate compounds having utility in the preparation of the aromatic polyanhydrides of the present invention. Therefore, according to another aspect of the present

15 invention, ortho-substituted bis-aromatic carboxylic acid anhydrides are provided having the structure of Formula II:



20 wherein Ar and R, and the preferred species thereof, are the same as described above with respect to Formula I and R is substituted on each Ar ortho to the anhydride group.

25 The present invention also includes ortho-substituted bis-aromatic dicarboxylic acids, which are novel and non-obvious intermediate compounds having utility in the preparation of ortho-substituted bis-aromatic carboxylic acid anhydrides. Therefore, according to another aspect of the

30 present invention, an ortho-substituted bis-aromatic dicarboxylic acid is provided having the structure of $\text{HOOC}-\text{Ar}-\text{R}-\text{Ar}-\text{COOH}$, wherein Ar and R, and the preferred species thereof, are the same as described above with respect to Formula I, and R is substituted on each Ar ortho to each

35 carboxylic acid group.

The aromatic polyanhydrides of the present invention meet

the need for moldable biocompatible biodegradable polymers. Therefore, the present invention also includes implantable medical devices containing the aromatic polyanhydrides of the present invention. When Ar and R are selected so that the aromatic polyanhydride hydrolyzes to form therapeutic salicyclates, the aromatic polyanhydrides have potential uses as biocompatible, biodegradable scaffolding implants for tissue reconstruction in which the degradation products have anti-thrombogenic qualities.

In addition, the aromatic polyanhydrides that hydrolyze to form therapeutic salicyclates have potential uses as anti-inflammatory dosage forms, including dosage forms for oral administration, particularly in the treatment of digestive disorders, including bowel disorders such as inflammatory bowel disease, Crohn's disease, and the like. Ar and R may also be selected so that the aromatic polyanhydrides hydrolyze to form therapeutic non-steroidal anti-inflammatory naphthyl and phenyl propionates that resemble compounds such as ibuprofen, ketoprofen, naproxen, and the like, and other aromatic anti-inflammatory compounds such as indomethacin, indoprofen, and the like.

Therefore, the present invention also includes a method for treating inflammation by administering to a patient in need thereof a quantity of the aromatic polyanhydride of the present invention in which Ar and R are selected so that aromatic polyanhydride hydrolyzes to form therapeutic salicyclates at the site of inflammation in an amount effective to relieve the inflammation. The aromatic polyanhydrides may be administered orally. This is particularly useful in the treatment of digestive inflammation, such as inflammatory bowel disease, because the therapeutic salicyclates are formed in the gastro-intestinal tract of the patient. Methods for treating inflammation with aromatic polyanhydrides that hydrolyze to form therapeutic naphthyl or phenyl propionates are included in the present invention as well, as well as methods for treating inflammation

with aromatic polyanhydrides that hydrolyze to form indomethacin or indoprofen.

The present invention therefore also includes anti-inflammatory oral dosage forms consisting essentially of the aromatic polyanhydrides of the present invention that hydrolyze to form therapeutic salicyclates or naphthyl or phenyl propionates, or indomethacin or indoprofen, and a pharmaceutically acceptable excipient. The oral dosage forms may further include a biologically or pharmaceutically active compound to be co-administered with the therapeutic degradation products.

Ar and R may also be selected so that the aromatic polyanhydrides hydrolyzes to form therapeutic antiulcerative drugs such as rosaprostol, therapeutic antifibrotic aminobenzoates and therapeutic vasoconstricting phenylethanolamines and vasoconstricting drugs such as midodrine. Therefore, the present invention also includes a method for therapeutic treatment by administering to a patient in need thereof a quantity of the aromatic polyanhydride of the present invention in which Ar and R are selected so that aromatic polyanhydride hydrolyzes to form rosaprostol, antifibrotic aminobenzoates, vasoconstricting phenylethanolamines and midodrine. The present invention also includes oral dosage forms consisting essentially of the aromatic polyanhydrides of the present invention in which Ar and R are selected so that the aromatic polyanhydrides hydrolyze to form rosaprostol, antifibrotic aminobenzoates, vasoconstricting phenylethanolamines and midodrine.

In another embodiment of the present invention, the aromatic polyanhydrides are combined with a quantity of biologically or pharmaceutically active compound sufficient for effective site-specific or systemic drug delivery as described by Gutkowsky et al., J. Biomater. Res., 29, 811-21 (1995) and Hoffman, J. Controlled Release, 6, 297-305 (1987). The biologically or pharmaceutically active compound may be physically admixed, embedded or dispersed in the polymer

matrix. Alternatively, derivatives of biologically and pharmaceutically active compounds can be attached to repeating units of the polymers of the present invention by covalent bonds linked to an Ar ring or an R organic moiety. This provides for sustained release of the biologically or pharmaceutically active compound.

Another aspect of the present invention provides a method for site-specific or systemic drug delivery by implanting in the body of a patient in need thereof an implantable drug delivery device containing a therapeutically effective amount of a biologically or pharmaceutically active compound in combination with an aromatic polyanhydride of the present invention.

A more complete appreciation of the invention and many more other intended advantages can be readily obtained by reference to the following detailed description of the preferred embodiments and claims, which disclose the principles of the invention and the best modes which are presently contemplated for carrying them out.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides aromatic polyanhydrides with improved degradation properties and processability having repeating units with the structure of Formula I in which Ar and R are the same as described above with respect to Formula I. R preferably has a structure of $-Z_1-R_1-Z_1-$, in which R_1 is a difunctional organic moiety and both Z_1 's are difunctional moieties independently selected from ethers, esters, amides, anhydrides, urethanes, carbamates, carbonates, sulfides, and the like. R_1 may be an alkylene group containing from 1 to 20, and preferably 6, carbon atoms, or R_1 may be a group having from 2 to 30, and preferably 6, carbon atoms having a structure selected from $(-CH_2-CH_2-O-)_m$, $(-CH_2-CH_2-CH_2-O-)_m$, and $(-CH_2-CH(CH_3)-O-)_m$, or R_1 may have the structure $-R_2-Z_2-R_3-$, wherein R_2 and R_3 are independently alkylene groups containing

from 1 to 19 carbon atoms or groups having from 2 to 18 carbon atoms having a structure selected from $(-\text{CH}_2-\text{CH}_2-\text{O}-)_m$, $(-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-)_m$, and $(-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{O}-)_m$, and Z_2 is selected from the difunctional moieties described above with respect to Z_1 .

5 Ar may be an alkylaryl group, in which a difunctional organic moiety is positioned between each anhydride carbonyl group and the corresponding aromatic ring. Preferably, however, each carbonyl group is directly substituted on the corresponding aromatic ring.

10 Preferred polymers of the present invention have repeating units with the structure of Formula I in which Ar is a phenyl ring and R is selected from $-\text{Z}_1-(\text{CH}_2)_n-\text{Z}_1-$, $-\text{Z}(\text{CH}_2-\text{CH}_2-\text{O})_m-\text{Z}_1-$, $-\text{Z}(\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O})_m-\text{Z}_1-$, and $-\text{Z}(\text{CH}_2-\text{CH}(\text{CH}_3)-\text{O})_m-\text{Z}_1-$, wherein Z_1 is an ether, ester or amide group and n is from 1 to 20 inclusive, and preferably is 6, and m is selected so that R has from 2 to 20, and preferably 6, carbon atoms.

20 The aromatic polyanhydrides of the present invention may be prepared by the method described in Conix, Macromol. Synth., 2, 95-99 (1996), in which dicarboxylic acids are acetylated in an excess of acetic anhydride at reflux temperatures followed by melt condensation of the resulting carboxylic acid anhydride at 180°C for 2-3 hours. The resulting polymers are isolated by precipitation into diethyl ether from methylene chloride. The described process is essentially the conventional method for polymerizing bis-aromatic dicarboxylic acid anhydrides into aromatic polyanhydrides.

30 Aromatic polyanhydrides in accordance with the present invention have weight average molecular weights of at least about 1500 daltons, up to about 35,000 daltons, calculated by Gel Permeation Chromatography (GPC) relative to narrow molecular weight polystyrene standards.

35 The aromatic polyanhydrides of the present invention are produced from orth-substituted bis-aromatic carboxylic acid anhydrides having the structure of Formula II in which Ar, R

and the preferred species thereof are the same as described above with respect to Formula I. As noted above, ortho-substituted bis-aromatic carboxylic acid anhydrides are prepared by acetylation of the corresponding ortho-substituted bis-aromatic carboxylic acids in an excess of acetic anhydride at reflux temperatures. The dicarboxylic acids have the structure of Formula III, wherein Ar, R and the preferred species thereof are the same as described above with respect to Formula I.

The dicarboxylic acids are prepared by reacting a stiochiometric ratio of aromatic carboxylic acid having the structure $Z_3\text{-Ar-COOH}$ and a compound having a structure $Z_4\text{-R-Z}_4$, wherein Ar is a substituted or unsubstituted aromatic ring on which Z_3 is substituted ortho to the carboxylic acid group, R is a difunctional organic moiety and Z_3 and Z_4 are functional groups selected to provide the linkage desired between the difunctional organic moiety and the two aromatic rings.

Suitable Z_3 and Z_4 functional groups, and the manner in which they may be reacted to produce the bis-aromatic dicarboxylic acids of the present invention, may be readily determined by those of ordinary skill in the art without undue experimentation. For example, for aromatic polyanhydrides having the structure of Formula I in which Ar is a phenyl group and R is $\text{-O-(CH}_2\text{)}_n\text{-O-}$, the ortho-substituted bis-aromatic dicarboxylic acid starting material may be prepared by reacting o-salicylic acid with 1,6-dibromohexane.

The aromatic polyanhydrides of the present invention can be isolated by known methods commonly employed in the field of synthetic polymers to produce a variety of useful articles with valuable physical and chemical properties. The new polymers can be readily processed by solvent casting to yield films, coatings, dishes and sponges with different geometric shapes for design of various medical implants, and may also be processed by compression molding and extrusion. Medical implant applications include the use of aromatic polyanhydrides to form shaped articles such as vascular graphs

and stents, bone plates, sutures, implantable sensors, implantable drug delivery devices, stents for tissue regeneration, and other articles that decompose harmlessly within a known time period.

5 The polymers of the present invention include aromatic polyanhydrides having a repeating unit with the structure of Formula I in which Ar and R are selected to provide aromatic polyanhydrides that hydrolyze to form therapeutically useful salicyclates. As noted above, the salicyclates may be
10 employed to treat inflammation, particularly digestive inflammation such as inflammatory bowel disorders. Thus, implantable or ingestible drug delivery devices of the present invention include oral dosage forms consisting essentially of the aromatic polyanhydrides of the present invention that
15 hydrolyze to form therapeutic salicyclates, in combination with a pharmaceutically acceptable excipient. The oral dosage forms function to deliver salicyclates to the site of inflammation, either directly, or by being absorbed into the bloodstream from the digestive tract. The salicyclates may be
20 supplemented with other therapeutic agents in the polymer matrix.

 Examples of the therapeutic salicyclates include, but are not limited to, thymotic acid, 4,4-sulfinyldianiline, 4-sulfanilamidosalicylic acid, sulfanilic acid,
25 sulfanilylbenzylamine, sulfaloxic acid, succisulfone, salicylsulfuric acid, salsallate, salicylic alcohol, orthocaine, mesalamine, gentisic acid, enfenamic acid, cresotic acid, aminosalicic acid, aminophenylacetic acid, acetylsalicic acid, and the like. The identification of Ar
30 and R moieties that provide aromatic polyanhydrides that hydrolyze to form such therapeutically useful salicyclates can be readily determined by those of ordinary skill in the art without undue experimentation.

 Ar and R may also be selected so that the aromatic
35 polyanhydrides hydrolyze to form therapeutic non-steroidal anti-inflammatory phenyl and naphthyl propionates,

indomethacin and indoprofen. The identification of Ar and R moieties that provide aromatic polyanhydrides that hydrolyze to form such therapeutic anti-inflammatory compounds can also be readily determined by those of ordinary skill in the art without undue experimentation.

Ar and R may also be selected so that the aromatic polyanhydrides hydrolyze to form other therapeutic compounds. For example, Ar and R may be selected to provide an aromatic polyanhydride that hydrolyzes to form the antiulcerative drug rosaprostol. Ar and R may also be selected to provide aromatic polyanhydrides that hydrolyze to form antifibrotic aminobenzoates. Ar and R may further be selected to provide polyanhydrides that hydrolyze to form the vasoconstricting drug midodrine, as well as vasoconstricting phenylethanolamines. Again, the identification of Ar and R moieties that provide aromatic polyanhydrides that hydrolyze to form such therapeutic compounds can readily be determined by those of ordinary skill in the art without undue experimentation.

Pharmaceutically acceptable excipients for oral administration are well known and include diluents such as lactose, sucrose, mannitol, sorbitol, cellulose, glycine, and the like, lubricants such as silica, talc, stearic acid and salts thereof, and the like, binders such as magnesium aluminum silicate, starches such as corn starch, methyl cellulose, and the like, and disintegrating agents such as starches, agar, and the like, as well as dyestuffs, flavors and sweeteners. The dosage forms are manufactured in a manner that is in itself well known, for example, by means of conventional mixing, granulating or dragee-making processes.

The quantity of aromatic polyanhydride that hydrolyzes to form an amount of therapeutic salicyclate effective to relieve inflammation can be readily determined by those of ordinary skill in the art without undue experimentation. The quantity essentially corresponds stiochiometrically to the amount of salicyclate known to produce an effective treatment. Oral

dosage forms of aromatic polyanhydrides that hydrolyze to form other therapeutic non-steroidal anti-inflammatory compounds and other therapeutic compounds are prepared and administered in a similar manner.

5 The ortho-substituted aromatic polyanhydrides of the present invention exhibit desirable adhesion to cell cultures. The disruption of crystallinity is believed to improve the attachment and growth of cells and may facilitate specific interactions with proteins, peptides and cells. The aromatic
10 polyanhydrides of the present invention are thus useful as scaffolding implants for tissue reconstruction. The polymer surfaces may also be modified by simple chemical protocols to attach specific peptides or to immobilize proteins to elicit selective cellular responses in tissue engineering
15 applications or in implant design.

 Controlled drug delivery systems may also be prepared, in which a biologically or pharmaceutically active agent is physically embedded or dispersed into the polymeric matrix, physically admixed with, or covalently bonded to the aromatic
20 polyanhydride. Covalent bonding is accomplished by providing an aromatic polyanhydride having reactive functional groups on one or more Ar groups or R moieties and reacting the polyanhydride with a derivatized or underivatized biologically or pharmaceutically active compound capable of reacting with
25 the functional group on the aromatic polyanhydride to form a covalent bond. Thus, biologically or pharmaceutically active compounds may be linked to aromatic polyanhydrides by means of ester groups, amide groups, and the like.

 Examples of biologically or pharmaceutically active
30 compounds suitable for the use in the present invention include acyclovir, cephradrine, malphalan, procaine, ephedrine, adriamycin, daunomycin, plumbagin, atropine, quinine, digoxin, quinidine, biologically active peptides, chlorin e₆, cephradrine, cephalothin, penicillin IV, nicotinic
35 acid, chemodeoxycholic acid, chlorambucil, and the like. Biologically active compounds, for the purposes of the present

invention, are additionally defined as including cell mediators, biologically active ligands, and the like. The compounds are covalently bonded to the aromatic polyanhydride by methods well understood by those of ordinary skill in the art. Drug delivery compounds may also be formed by physically blending the biologically or pharmaceutically active compound to be delivered with the aromatic polyanhydrides of the present invention using conventional techniques well-known to those of ordinary skill in the art.

The following non-limiting examples set forth hereinbelow illustrate certain aspects of the invention. All parts and percentages are by weight unless otherwise noted and all temperatures are in degrees Celsius. Except for acetic anhydride and ethyl ether (Fisher Scientific), all solvents and reagents were obtained from Aldrich Chemical. All solvents were HPLC grade. All other reagents were of analytical grade and were purified by distillation or recrystallization.

All compounds were characterized by a proton nuclear magnetic resonance (NMR) spectroscopy, infrared (IR) spectroscopy, gel permeation chromatography (GPC), high performance liquid chromatography (HPLC), differential scanning calorimetry (DSC), and thermal gravimetric analysis (TGA). Infrared spectroscopy was performed on an AT1 Mattson Genesis (M100) FTIR Spectrophotometer. Samples were prepared by solvent casting on NaCl plates. ^1H and ^{13}C NMR spectroscopy was obtained on a Varian 200 MHz or Varian 400 MHz spectrometer in solutions of CDCl_3 or $\text{DMSO}-d_6$ with solvent as the internal reference.

GPC was performed on a Perkin-Elmer Advanced LC Sample Processor (ISS 200) with PE Series 200 LC Pump and a PE Series LC Refractive Index Detector to determine molecular weight and polydispersity. The data analysis was carried out using Turbochrom 4 software on a DEC Celebris 466 computer. Samples were dissolved in tetrahydrofuran and eluted through a mixed bed column (PE PL gel, 5 μm mixed bed) at a flow rate of 0.5

mL/min. Samples (about 5 mg/mL) were dissolved into the tetrahydrofuran and filtered using 0.5 μ m PTFE syringe filters prior to column injection. Molecular weights were determined relative to narrow molecular weight polystyrene standards (Polysciences, Inc.).

Thermal analysis was performed on a Perkin-Elmer system consisting of a TGA 7 thermal gravimetric analyzer equipped with PE AD-4 autobalance and Pyris 1 DSC analyzer. Pyris software was used to carry out data analysis on a DEC Venturis 5100 computer. For DSC, an average sample weight of 5-10 mg was heated at 10°C/min. at a 30 psi flow of N₂. For TGA, an average sample weight of 10 mg was heated at 20°C/min under a 8 psi flow of N₂. Sessile drop contact angle measurements were obtained with an NRL Goniometer (Rame-hart) using distilled water. Solutions of polymer in methylene chloride (10% wt/vol.) were spun-coated onto glass slips, at 5,000 rpm for 30 seconds.

EXAMPLES

Example I-Preparation of 1,6-Bis(o-Carboxyphenoxy) Hexane Dicarboxylic Acid

To a mixture of salicylic acid (77.12 g, 0.5580 mole) and distilled water (84mL) sodium hydroxide (44.71 g, 1.120 mole) was added. The reaction was brought to reflux temperature before 1,6-dibromohexane (45.21 g, 0.2790 mole) was added drop-wise. Reflux was continued for 23 hours after which additional sodium hydroxide (11.17 g, 0.2790 mole) was added. The mixture was refluxed for 16 more hours, cooled, filtered, and washed with methanol. The yield was 48.8%.

Example II-Preparation of 1,6-Bis(o-Carboxyphenoxy) Hexane Monomer (o-CPH)

The dicarboxylic acid of Example I was acetylated in an excess of acidic anhydride at reflux temperature. The resulting monomer was precipitated from methylene chloride

into an excess of diethyl ether. The yield was 66.8%.

Example III-Preparation of Poly(1,6-Bis(o-Carboxyphenoxy) Hexane) (Poly(o-CPH))

5 The monomer of Example II was polymerized in a melt
condensation performed at 180°C for 3 hours under vacuum in a
reaction vessel with a side arm. The polymerization vessel
was flushed with nitrogen at frequent intervals. The polymer
was isolated by precipitation into diethyl ether from
10 methylene chloride. The yield was quantitative.

All compounds were characterized by nuclear magnetic
resonance spectroscopy, GPC, differential scanning calorimetry
(DSC), thermal gravimetric analysis, contact angle
measurements, UV spectroscopy, mass spectroscopy, elemental
15 analysis and high pressure liquid chromatography (HPLC).

The o-CPH monomer was polymerized by melt
polycondensation for 60 minutes at temperatures ranging from
100° to 300°C. Analysis of the resulting polymers by GPC
indicated that the highest molecular weight, coupled with the
20 lowest polydispersity index occurred at 260°C.

The poly(o-CPH) was generally soluble in methylene
chloride and chloroform, while the poly(p-CPH) was not. The
poly(o-CPH) was slightly soluble in tetrahydrofuran, acetone
and ethyl acetate.

25 Disks of poly(o-CPH), poly(p-CPH) and, as a reference,
poly(lactic acid glycolic acid) were prepared and placed in
0.1 phosphate buffer solution at 37°C for 4 weeks. The
degradation media was replaced periodically. The degradation
profile was linear up to three weeks time.

30 In currently used polyanhydride systems, the aromatic
groups are para-substituted. This substitution pattern
results in higher melt and glass transition temperatures and
decreased solubility, thus ultimately making these para-
substituted polymers difficult to process.

35 Poly(o-CPH), unlike poly(p-CPH), has both a lower melting
point (65°C vs. 143°C) and glass transition temperature (35°C

vs. 47°C). It is also possible to solution cast poly(o-CPH) using low-boiling solvents whereas poly(p-CPH) is relatively insoluble in most organic and aqueous solvents. This structural modification gives a polymer whose hydrolysis products are chemically similar to aspirin. Aspirin is an anti-inflammatory agent derived from salicylic acid, which is one of the reagents used to synthesize the inventive polyanhydrides. Therefore, the degradation products of this polymer may actually aid in patient recovery. Because of pliability and ease of processing, the aromatic polyanhydrides of the present invention have great potential as polymer scaffolds for wound healing.

Example IV-Preparation of 1,3-bis(o-carboxyphenoxy)propane dicarboxylic acid

1,3-dibromopropane (14.7 mL, 0.145 mole) was added to a mixture of salicylic acid (40.0 g, 0.290 mole), distilled water (44 mL) and sodium hydroxide (23.2 g, 0.580 mole) using the method described in Example I. After 4 hours, additional sodium hydroxide (5.79 g, 0.145 mole) was added to the reaction mixture. Reflux was continued for another 4 hours, after which the mixture was cooled, filtered and washed using the methods described in Example I. The yield was 37.7%

Example V-Preparation of poly(1,3-bis(o-carboxyphenoxy)propane)

The dicarboxylic acid of Example IV was acetylated using the methods of Example II. The acetylated dicarboxylic acid was then polymerized using the methods described in Example III. The resulting polymer had a M_n of 8,500 daltons and a polydispersity of 2.3.

Contact angle measurements on solvent-cast films demonstrated that the hexyl chain of the polymer of Example III increased the surface hydrophobicity relative to the shorter propyl chain of the polymer of Example V. A comparison of thermal characteristics emphasized the effects

of lengthening the alkyl chain. In particular, the polymer of Example III has a T_g of 34°C and a T_d of 410°C, while the polymer of Example V had a T_g of 50°C and a T_d of 344°C. Thus, the hexyl chain decreased the glass transition temperature (T_g) relative to the propyl chain, reflecting the increased flexibility of the polymer chain. The opposite trend was observed for decomposition temperatures (T_d), with the longer alkyl chain increasing the T_d .

Optimum polycondensation conditions were determined for the polymer of Example III. Optimum conditions were defined as those that yielded a crude polymer with the highest molecular weight and highest T_g . Higher reaction temperatures decreased the M_n values (measured by GPC) with a concurrent increase in polydispersity. As expected for a condensation polymerization, longer reaction times yielded polymers with higher molecular weights. However, over longer reaction times, there appeared a subsequent decrease in T_g . Based on these results, the optimum conditions were defined as temperatures of 220°C for 150 minutes under a vacuum.

Example VI-Preparation of 1,8-bis[o-(benzylcarboxy)carboxy phenyl] octane dicarboxylic acid ester

The initial synthesis of poly(anhydride-ester) dicarboxylic acid monomers was attempted using the same methodology used for the poly(anhydride-ether) dicarboxylic monomers of Example III. It was found, however, that the reactivity of the phenol was enhanced by benzylation of the carboxylic acid group. In addition, the solubility of benzyl salicylate in organic media increased the ability of the reaction to move forward.

Thus, benzyl salicylate (1.530 g, 6.720 mmole) and distilled tetrahydrofuran were combined under an inert atmosphere in a reaction flask. An ice-salt bath was placed under the reaction flask and the addition of 60% sodium hydride (0.4840 g, 12.10 mmole) followed. After one hour, sebacyl chloride (0.7850 g, 3.280 mmole) was added drop-wise

to the 0°C reaction mixture. After 30 minutes, the reaction mixture was vacuum filtered, the filtrate collected and the solvent removed to reveal to yield the free carboxylate as a white solid residue. Purification was performed using a chromatron with ethyl acetate/methylene chloride (20/80) as the solvent system. The yield was 43%.

Example VII-Polymerization of Poly(1,8-bis(o-dicarboxyphenyl) octane)

To remove the benzyl protecting groups, the 1,8-bis[(benzylcarboxy)carboxyphenyl]octane dicarboxylic acid ester of Example VI (0.06000 g, 0.9620 mmole) was dissolved in methylene chloride in a reaction flask (60.00 mL). The catalyst Pd-C (10%, 1.200 g) was added to the reaction flask. After 30 minutes, the reaction was complete. The reaction mixture was filtered and the solvent removed to yield the free dicarboxylic acid as a white solid residue which was recrystallized using petroleum ether and methylene chloride. The yield was 45%.

The dicarboxylic acid was acetylated using the methods described in Example II and the acetylated dicarboxylic acid was then polymerized using the methods described in Example III. The resulting polymer had a M_w of 3,000 daltons and a polydispersity of 1.40.

Subsequent polymerizations yielded polymers with M_w 's ranging from 2,000 to 5,000 daltons with corresponding polydispersities of approximately 1.40.

The poly(anhydride esters) of Example VII were compression molded into circular discs and placed in phosphate buffered saline solution under acidic, neutral and basic conditions. Over the course of a three-week degradation study, the polymers in the acidic and neutral solutions showed no observable changes, whereas the polymer in the basic media showed significant morphological changes over time.

Example VIII-Preparation of Poly[(1,8-bis(o-dicarboxyphenyl) octane)-(1,6-bis(p-carboxyphenoxy) hexane] copolymers

5 The 1,8-bis(o-dicarboxyphenyl) octane of Example II was copolymerized with 1,6-bis(p-carboxyphenoxy) hexane using the methods described in Example III. In an in vivo mouse study, each mouse was implanted with 2 polymers, the copolymer of Example VIII and poly(1,6-bis(p-carboxyphenoxy)hexane). Each polymer was compression molded for 1 to 5 minutes at 1 to 20 K psi depending on the thickness of polymer needed. The polymer was placed under the palatal gingival mucosa adjacent to the first maxillary molars. The mice were sacrificed at 1, 4 and 10 day intervals and demonstrated the biocompatibility and biodegradability in vivo of the polymers of the present invention, with salicylic acid being released upon degradation, via hydrolysis of the polymer backbone.

STATEMENT OF INDUSTRIAL APPLICABILITY

20 The polymers of the present invention have a variety of pharmaceutical applications, particularly as anti-inflammatory compounds.

25 The foregoing examples and description of the preferred embodiment should be taken as illustrating, rather than as limiting, the present invention as defined by the claims. As would be readily appreciated, numerous variations and combinations of the features set forth above can be utilized without departing from the present invention as set forth in the claims. Such variations are not regarded as a departure from the spirit and the scope of the invention, and all such variations are intended to be included within the scope of the following claims.

WHAT IS CLAIMED IS:

1. An aromatic polyanhydride comprising a repeating
 5 unit having the structure:



10 wherein Ar is a substituted or unsubstituted aromatic ring and R is a difunctional organic moiety substituted on each Ar ortho to the anhydride group.

15 2. The aromatic polyanhydride of claim 1, wherein Ar is a phenyl group and R is $-\text{Z}_1-\text{R}_1-\text{Z}_1-$, wherein R_1 is a difunctional organic moiety and Z_1 is a difunctional moiety selected from the group consisting of ethers, ester, amides, urethanes, carbamates and carbonates.

20 3. The aromatic polyanhydride of claim 2, wherein Z_1 is an ether, ester or amide group, and R_1 is selected from the group consisting of $(-\text{CH}_2-)_n$, $(-\text{CH}_2-\text{CH}_2-\text{O}-)_m$, $(-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-)_m$, and $(-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{O}-)_m$, wherein n is from 1 to 20, inclusive and m is selected so that R_1 has between 2 and 20 carbon atoms,
 25 inclusive.

4. The aromatic polyanhydride of claim 3, wherein n is
 6.

30 5. The aromatic polyanhydride of claim 2, wherein R_1 is $-\text{R}_2-\text{Z}_2-\text{R}_3-$, wherein R_2 and R_3 are difunctional organic moieties and Z_2 is a difunctional moiety selected from the group consisting of ethers, esters, amides, urethanes, carbamates and carbonates.

35

6. The aromatic polyanhydride of claim 5, wherein R_2 and R_3 are independently selected from the group consisting of alkylene groups containing from 1 to 19 carbon atoms, $(-CH_2-CH_2-O-)_n$, $(-CH_2-CH_2-CH_2-O-)_n$, and $(-CH_2-CHCH_3-O-)_m$, wherein m is between 2 and 18, inclusive.

7. The aromatic polyanhydride of claim 1, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form therapeutic salicylates, non-steroidal anti-inflammatory naphthyl or phenyl propionates, indomethacin, indoprofen, rosaprostal, antifibrotic aminobenzoates, midodrine, or vasoconstricting phenylethanolamines.

8. The aromatic polyanhydride of claim 7, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form a therapeutic salicylate selected from the group consisting of thymotic acid, 4,4-sulfinyldinailine, 4-sulfanilamidosalicylic acid, sulfanilic acid, sulfanilylbenzylamine, sulfaloxic acid, succisulfone, salicylsulfuric acid, salsallate, salicylic alcohol, orthocaine, mesalamine, gentisic acid, enfenamic acid, cresotic acid, aminosalicic acid, aminophenylacetic acid and acetylsalicic acid.

9. The aromatic polyanhydride of claim 7, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form therapeutic non-steroidal anti-inflammatory naphthyl or phenyl propionates selected from the group consisting of ibuprofen, ketoprofen and naproxin.

10. An implantable medical device comprising the aromatic polyanhydride of claim 1.

11. The implantable medical device of claim 10, wherein said device is a scaffolding implant for tissue reconstruction.

5 12. The implantable medical device of claim 10 comprising a biologically or pharmaceutically active compound in combination with said aromatic polyanhydride, wherein said active compound is present in amounts sufficient for therapeutically effective site-specific or systemic drug
10 delivery.

13. The implantable medical device of claim 12, wherein said biologically or pharmaceutically active compound is covalently bonded to said aromatic polyanhydride.

15 14. A method for site-specific or systemic drug delivery comprising implanting in the body of a patient in need thereof an implantable drug delivery device comprising a therapeutically effective amount of a biologically or
20 pharmaceutically active compound in combination with the aromatic polyanhydride of claim 1.

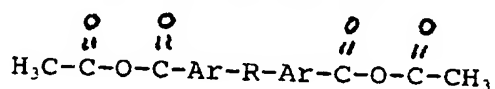
15 15. The method of claim 14, wherein said biologically or pharmaceutically active compound is covalently bonded to said aromatic polyanhydride.

16. A drug delivery system comprising the aromatic polyanhydride of claim 1 physically admixed with a biologically or pharmaceutically active agent.

30 17. A drug delivery system comprising a biologically or pharmaceutically active agent physically embedded or dispersed into a polymeric matrix formed from the aromatic polyanhydride of claim 1.

18. A drug delivery system comprising a biologically or pharmaceutically active agent covalently bonded to the aromatic polyanhydride of claim 1.

5 19. An ortho-substituted bis-aromatic dicarboxylic acid anhydride having the structure:



10 wherein Ar is a substituted or unsubstituted aromatic ring and R is a difunctional organic moiety substituted on each Ar ortho to the anhydride group.

15 20. The acid anhydride of claim 19, wherein Ar is a phenyl group and R is $-\text{Z}_1-\text{R}_1-\text{Z}_1-$, wherein R_1 is a difunctional organic moiety and Z_1 is a difunctional moiety selected from the group consisting of ethers, esters, amides, urethanes, carbamates and carbonates.

20 21. The acid anhydride of claim 20, wherein Z_1 is an ether, ester or amide group, and R_1 is selected from the group consisting of $(-\text{CH}_2)_n$, $(-\text{CH}_2-\text{CH}_2-\text{O}-)_m$, $(-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{O}-)_m$, and $(-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{O}-)_m$, wherein n is from 1 to 20, inclusive, and m is selected so that R_1 has between 2 and 20 carbon atoms, inclusive.

22. The acid anhydride of claim 21, wherein n is 6.

30 23. An ortho-substituted bis-aromatic dicarboxylic acid having the structure $\text{HOOC}-\text{Ar}-\text{R}-\text{Ar}-\text{COOH}$, wherein Ar is a substituted or unsubstituted aromatic ring and R is a difunctional organic moiety on both Ar rings ortho to each carboxylic acid group.

35 24. The dicarboxylic acid of claim 23, wherein Ar is a phenyl group and R is $-\text{Z}_1-\text{R}_1-\text{Z}_1-$, wherein R_1 is a difunctional

organic moiety and Z_1 is a difunctional organic moiety selected from the group consisting of ethers, esters, amides, urethanes, carbamates and carbonates.

5 25. The dicarboxylic acid of claim 24, wherein Z_1 is an ether, ester or amide group, and R_1 is selected from the group consisting of $(-CH_2)_n$, $(-CH_2-CH_2-O-)_m$, $(-CH_2-CH_2-CH_2-O-)_m$ and $(-CH_2-CH(CH_3)-O-)_m$, wherein n is from 1 to 20, inclusive, and m is selected to that R_1 has between 2 and 20 carbon atoms,
10 inclusive.

26. The dicarboxylic acid of claim 25, wherein n is 6.

15 27. A method for treating inflammation comprising administering to a patient in need thereof a quantity of the aromatic polyanhydride of claim 1, Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form therapeutic salicylates, phenyl or naphthyl propionic acids, indomethacin or indoprofen at the site of said inflammation in
20 an amount effective to relieve said inflammation.

28. The method of claim 27, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form a therapeutic salicylate selected from the group
25 consisting of thymotic acid, 4,4-sulfinyldianiline, 4-sulfanilamidosalicylic acid, sulfanilic acid, sulfanilylbenzylamine, sulfaloxic acid, succisulfone, salicylsulfuric acid, salsallate, salicylic alcohol, orthocaine, mesalamine, gentisic acid, enfenamic acid,
30 cresotic acid, aminosalicic acid, aminophenylacetic acid and acetylsalicic acid.

29. The method of claim 27, wherein Ar and Z are selected so that said aromatic polyanhydride hydrolyzes to form therapeutic non-steroidal anti-inflammatory naphthyl or phenyl propionates selected from the group consisting of
5 ibuprofen, ketoprofen and naproxin.

30. The method of claim 27, wherein said aromatic polyanhydride is administered orally.

10 31. A therapeutic method comprising administering to a patient in need thereof an effective amount of an aromatic polyanhydride according to claim 1, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form rosaprostol, antifibrotic aminobenzoates, midodrine or
15 vasonconstricting phenylethanalamines.

32. The method of claim 31, wherein said aromatic polyanhydride is administered orally.

20 33. An anti-inflammatory oral dosage form consisting essentially of an effective amount of the aromatic polyanhydride of claim 1, and a pharmaceutically acceptable excipient, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form therapeutic salicylates,
25 phenyl or naphthyl propionic acids, indomethacin, or indoprofen.

30 34. The oral dosage form of claim 33, wherein Ar and R are selected so that said aromatic polyanhydride hydrolyzes to form a therapeutic salicylate selected from the group consisting of thymotic acid, 4,4-sulfinyldiniline, 4-sulfanilamidosalicylic acid, sulfanilic acid, sulfanilylbenzylamine, sulfaloxic acid, succisulfone,
35

salicylsulfuric acid, salsallate, salicylic alcohol, orthocaine, mesalamine, gentisic acid, enfenamic acid, cresotic acid, aminosalicic acid, aminophenylacetic acid and acetylsalicic acid.

5

35. The oral dosage form of claim 33, wherein Ar and Z are selected so that said aromatic polyanhydride hydrolyzes to form therapeutic non-steroidal anti-inflammatory naphthyl or phenyl propionates selected from the group consisting of
10 ibuprofen, ketoprofen and naproxin.

36. The oral dosage form of claim 33, further comprising a second therapeutic agent to be administered in combination with said polyanhydride.

15

37. A method for treating digestive inflammation comprising orally administering to a patient in need thereof a quantity of the aromatic polyanhydride of claim 1, wherein Ar and R are selected so that said aromatic polyanhydride
20 hydrolyzes to form therapeutic salicylates at the site of said inflammation in an amount effective to relieve said inflammation.

38. The method of claim 37, wherein said therapeutic
25 salicylate is selected from the group consisting of thymotic acid, 4,4-sulfinyldiniline, 4-sulfanilamidosalicylic acid, sulfanilic acid, sulfanilylbenzylamine, sulfaloxic acid, succisulfone, salicylsulfuric acid, salsallate, salicylic alcohol, orthocaine, mesalamine, gentisic acid, enfenamic
30 acid, cresotic acid, aminosalicic acid, aminophenylacetic acid and acetylsalicic acid.

39. A therapeutic treatment method comprising
administering to a patient in need thereof an effective
35 quantity of an aromatic polyanhydride according to claim 1, wherein Ar and R are selected so that said aromatic

polyanhydride hydrolyzes to form rosaprostal, antifibrotic aminobenzoates, midodrine, or vasoconstricting phenylethanolamines.

- 5 40. The method of claim 39, wherein said aromatic polyanhydride is administered orally.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/18816

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : CO8G 63/00, 63/02, 67/00, 69/00

US CL : 528/176, 193, 271, 272

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 528/176, 193, 271, 272

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,264,540 A (COOPER ET AL.) 23 November 1993 (23-11-93), abstract, column 5 lines 5-55, column 6 lines 5-55	1-40
X	US 4,997,904 A (DOMB) 05 March 1991 (05-03-91), abstract, column 2 Lines 5-55, column 4 Line 5-30.	1-40



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

14 DECEMBER 1998

Date of mailing of the international search report

14 JAN 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

TERRESSA MOSLEY

Telephone No. (703) 308-0651

THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)